## *N*-Vinyl-1,3-oxazolidine-2-thiones as Dienophiles in Inverse Hetero-Diels–Alder Reactions: New Prospects for Asymmetric Induction

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**Abstract:** Several *N*-vinyl-1,3-oxazolidine-2-thione (*N*-vinyl OZT) were conveniently used as new dienophiles in Eu(fod)<sub>3</sub>-catalyzed reverse hetero-Diels–Alder reactions involving benzylidene pyruvic acid methyl ester. Simple chiral *N*-vinyl OZT analogues homogeneously led to moderate *endo* and facial diastereoselectivities, when compared to those obtained with the corresponding *N*-vinyl-1,3-oxazolidin-2-ones. In contrast, high diastereocontrols were observed with a sugar-derived *N*-vinyl OZT.

Key words: oxazolidinethiones, hetero-Diels-Alder, enamide

*N*-Vinyloxazolidinones **1** were recently described as new promising chiral dienophiles in inverse hetero-Diels-Alder reactions towards activated 1-oxabutadienes, leading with high diastereocontrol to heteroadducts 2 under Eu(fod)<sub>3</sub>-catalyzed conditions.<sup>1</sup> An efficient route to enantiopure N-(2-deoxyglycosyl)oxazolidinones 3 resulted from this approach. Compounds 3 appeared as the first representatives of a new class of de novo synthesized 2deoxy N-glycosides bearing an amino acid derivative as the aglycon. However, hydrolytic or reductive removal of the carbamate moiety in **3** proved to be troublesome.<sup>2</sup> For that reason, we considered that extending the scope of the hetero-Diels-Alder reactions to other relevant enamides such as N-vinyl-1,3-oxazolidine-2-thiones (N-vinyl OZT) 4 would be of much interest.<sup>3</sup> OZT heterocycles are useful synthons that can be specifically functionalized<sup>4</sup> and moreover, they are emerging as new chiral auxiliaries with high potential in chirality transfer.<sup>5</sup> Our laboratory has developed an efficient process based on a two-step sequence using the BPSE [1,2-bis(phenylsulfonyl)ethylene] methodology, which has shown a great efficiency on simple, chiral and carbohydrate-derived OZTs (Figure 1).<sup>6,7</sup>



Figure 1

SYNLETT 2006, No. 9, pp 1425–1427 Advanced online publication: 22.05.2006 DOI: 10.1055/s-2006-939722; Art ID: D00206ST © Georg Thieme Verlag Stuttgart · New York With a view to exploring the potential of these *N*-vinyl cyclic thionocarbamates, we first selected the achiral parent OZT **4a** ( $\mathbf{R}^1 = \mathbf{R}^2 = \mathbf{H}$ )<sup>7</sup> together with representative chiral substituted OZTs **4b**–**h**. These chiral *N*-vinyl OZTs were efficiently prepared in 44–74% yields according to the recently described two-step Michael addition–reductive elimination sequence (Scheme 1, Table 1).<sup>6</sup>





 Table 1
 Preparation of Chiral N-Vinyl OZTs 4b-e

N-Vinyl OZT	$\mathbb{R}^1$	$\mathbb{R}^2$	R <sup>3</sup>	Overall yield	
<b>4h</b> (4 <b>R</b> )	Ft	н	н	64	
<b>4c</b> (4 <i>S</i> )	Bn	Н	Н	74	
<b>4d</b> (4 <i>R</i> )	Bn	Н	Н	65	
<b>4e</b> (4 <i>S</i> )	Ph	Н	Н	51	
<b>4f</b> (4 <i>R</i> )	Ph	Н	Н	44	
<b>4g</b> (4 <i>S</i> ,5 <i>R</i> )	Me	Ph	Н	69	
4h	Me	Н	Me	64	

<sup>a</sup> After purification over silica gel.

Compounds **4** were reacted with benzylidenepyruvic acid methyl ester **5** (Scheme 2). Under the standard conditions previously used with *N*-vinyloxazolidinone **1** [refluxing cyclohexane, catalyst: 5 mol% Eu(fod)<sub>3</sub>],<sup>8</sup> *N*-vinyl OZT **4a** was smoothly converted in 56% yield into the heteroadduct **6a** with a moderate *endo*-selectivity (entry 1). Under similar conditions, the chiral *N*-vinyl OZTs **4b–h** exhibited a fair reactivity, giving rise to adducts **6b–h** in consistently good yields (75–87%, entries 2–7). Steric hindrance encountered in **4g** (entry 8) caused a considerable lowering of the yield but without interfering much in the stereochemical outcome.

The observed stereoselectivities with these new chiral dienophiles proved not to be higher than those observed in oxazolidinone series. After careful identification of *cis*-





## Scheme 2

and *trans*-isomers by NMR, the *endo*-selectivities of the cycloadditions were evaluated to range around 4:1, and the facial selectivity for *endo*-adducts did not exceed 3:1.

When compared to the results obtained with type-2 adducts (Figure 1, R = Ph),<sup>1</sup> such a stereochemical outcome seems to indicate that the nature of the cyclic moiety of the dienophile (carbamate versus thionocarbamate) would significantly influence both stereochemical parameters of the hetero-cycloaddition by a favorable versus disfavorable interaction with the lanthanide salt in the transition state (Table 2).

The vinyl bis-sulfone methodology has also proven efficient for the *N*-vinylation of complex bicyclic thionocarbamates such as branched, fused and spiranic sugarderived OZTs.<sup>9</sup> The chiral spiro *N*-vinyl OZT **7** was thus conveniently prepared from D-glucose in its two epimeric forms (**7a**,**b**) and tested in the cycloaddition study (Scheme 3).

Heterocycloaddition of **7b** and heterodiene **5** proceeded in low yields, albeit with a high *endo*-selectivity, whereas facial selectivity remained moderate (77:23) in the range of previous values. On the contrary, reacting **7a** with **5** gave a remarkably good yield of the desired heteroadduct **8** with a high selectivity for the *endo*-diastereomer in addition to a very good (90:10) facial selectivity.<sup>10,11</sup>





This enhanced facial diastereoselectivity compares well with previous results observed in the use of carbohydratebased vinyl ethers as chiral dienophiles towards heterodienes related to **5** under similar conditions.<sup>12</sup> The efficient chiral transfer in the synthesis of **8** could mainly be attributed to the specific architecture of the 1,2:5,6-di-*O*isopropylidene- $\alpha$ -D-glucofuranose moiety. In these cases, the chirality is anchored on carbon 5 of the OZT while with classical oxazolidinones, oxazolidinethiones and thiazolidinethiones carbon 4 is the chirality center encountered. Those first results open the development of well-defined spiro-carbohydrate templates towards improved auxiliaries for chirality transfer.

Table 2 Eu(fod)<sub>3</sub>-Catalyzed Heterocycloaddition of N-Vinyl OZTs 4a-e with 5

Entry	4	$\mathbf{R}^1$	$\mathbb{R}^2$	R <sup>3</sup>	Time (h)	6	Yield (%)	endo/exo	endo I/endo II	exo I/exo II
1	<b>4</b> a	Н	Н	Н	48	6a	56	86:14	-	_
2	<b>4b</b> (4 <i>R</i> )	Et	Н	Н	48	6b	75	78:22	72:28	74:26
3	<b>4c</b> (4 <i>S</i> )	Bn	Н	Н	48	6c	78	81:19	71:29	100:0
4	<b>4d</b> (4 <i>R</i> )	Bn	Н	Н	48	6d	87	86:14	27:73	0:100
5	<b>4e</b> (4 <i>S</i> )	Ph	Н	Н	48	6e	75	80:20	74:26	84:16
6	<b>4f</b> (4 <i>R</i> )	Ph	Н	Н	48	6f	82	75:25	72:28	61:39
7	<b>4g</b> (4 <i>S</i> ,5 <i>R</i> )	Me	Ph	Н	48	6g	77	89:11	54:46	75:25
8	4h	Н	Me	Me	48	6h	20	70:30	_	_

<sup>a</sup> After purification over silica gel.

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- (10) Compound **8** *endo I*:  $[a]_D^{20}$ +50 (*c* 1.0, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.33, 1.36, 1.47 (3 s, 12 H, CH<sub>3</sub>), 1.85 (dt,

 $\begin{array}{l} J_{\rm AB} = 12.8~{\rm Hz}, J_{2ax'.3'} = J_{2ax'-1'} = 11.3~{\rm Hz}, 1~{\rm H}, {\rm H}_{2ax'}), 2.36 \\ ({\rm (ddt}, J_{\rm AB} = 12.8~{\rm Hz}, J_{2eq'.3'} = 6.3~{\rm Hz}, J_{2eq'.1'} = J_{2eq'.4'} = 1.8~{\rm Hz}, \\ 1~{\rm H}, {\rm H}_{2eq'}), 3.38~{\rm (d}, J_{\rm AB} = 10.0~{\rm Hz}, 1~{\rm H}, {\rm H}_{7b}), 3.79~{\rm (s}, 3~{\rm H}, \\ {\rm H}_{7}), 3.80-4.00~{\rm (m}, 2~{\rm H}, {\rm H}_{6b}, {\rm H}_{3'}), 4.17-4.80~{\rm (m}, 4~{\rm H}, {\rm H}_{4}, {\rm H}_{5}, \\ {\rm H}_{6a}, {\rm H}_{7a}), 4.38~{\rm (d}, J_{2-1} = 3.5~{\rm Hz}, 1~{\rm H}, {\rm H}_{2}), 5.70~{\rm (d}, J_{1-2} = 3.5~{\rm Hz}, 1~{\rm H}, {\rm H}_{1}), 6.20~{\rm (t}, J_{4'.3'} = J_{4'.2eq'} = 1.6~{\rm Hz}, 1~{\rm H}, {\rm H}_{4'}), 6.29~{\rm (dd}, J_{1'.2ax'} = 11.3~{\rm Hz}, J_{1'.2eq'} = 1.8~{\rm Hz}, 1~{\rm H}, {\rm H}_{1'}), 7.18-7.41~{\rm (m}, 5~{\rm H}, {\rm H}\text{-arom.})~{\rm ppm}^{-13}{\rm C}~{\rm NMR}~{\rm (CDCl}_3); ~\delta = 25.1, 26.6, \\ 26.8, 31.1~{\rm (CH}_3), 34.4~{\rm (C-2')}, 38.6~{\rm (C-3')}, 47.0~{\rm (C-7)}, 52.4~{\rm (C-7')}, 68.2~{\rm (C-6)}, 73.2~{\rm (C-5)}, 77.4~{\rm (C-4)}, 83.5~{\rm (C-3)}, 83.9~{\rm (C-2)}, 88.3~{\rm (C-1')}, 103.2~{\rm (C-1)}, 110.5,~{\rm (CIV-iPrd)}, 114.4~{\rm (C-4')}, 114.9~{\rm (CIV-iPrd)}, 127.2~{\rm (C-o')}, 127.5~{\rm (C-p')}, 129.1~{\rm (C-m')}, 142.0~{\rm (C-n')}, 144.0~{\rm (C-5')}, 162.4~{\rm (C-6')}, 186.8~{\rm (C=S)}~{\rm ppm}.~{\rm MS}~{\rm (IS)}:~m/z = 548.5~{\rm [M+H]^+}. \end{array}$ 

- (11) Compound **8** endo II:  $[a]_{D}^{20} 26$  (c 0.5, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 1.17, 1.37, 4.41, 1.62$  (4 s, 12 H, CH<sub>3</sub>), 1.86 (dt,  $J_{AB} = 12.8$  Hz,  $J_{2ax'-3'} = J_{2ax'-1'} = 11.3$  Hz, 1 H,  $H_{2ax'}$ ), 2.37 (ddt,  $J_{AB} = 12.8$  Hz,  $J_{2eq'-3'} = 6.5$  Hz,  $J_{2eq'-1'} = J_{2eq'-4'} = 1.8$  Hz, 1 H,  $H_{2eq'}$ ), 3.69 (d,  $J_{AB} = 10.3$  Hz, 1 H,  $H_{7b}$ ), 3.82 (s, 3 H, H<sub>7</sub>), 3.90–4.00 (m, 4 H, H<sub>3</sub>', H<sub>5</sub>, H<sub>7a</sub>, H<sub>6b</sub>), 4.09 (dd,  $J_{AB} = 7.3$ Hz,  $J_{6a-5} = 2.8$  Hz, 1 H, H<sub>6a</sub>), 4.17 (d,  $J_{4-5} = 8.5$  Hz, 1 H, H<sub>4</sub>), 4.59 (d,  $J_{2-1} = 3.5$  Hz, 1 H, H<sub>2</sub>), 5.71 (d,  $J_{1-2} = 3.5$  Hz, 1 H, H<sub>1</sub>), 6.21 (t,  $J_{4'-3'} = J_{4'-2eq'} = 1.6$  Hz, 1 H, H<sub>4</sub>'), 6.32 (dd,  $J_{1'-2ax'} = 11.3$  Hz,  $J_{1'-2eq'} = 1.8$  Hz, 1 H, H<sub>1</sub>'), 7.18–7.40 (m, 5 H, H-arom.) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta = 25.4, 26.6, 27.0,$ 31.1 (CH<sub>3</sub>), 33.7 (C-2'), 38.6 (C-3'), 46.6 (C-7), 52.5 (C-7'), 68.6 (C-6), 73.9 (C-5), 77.4 (C-4), 84.0 (C-2), 84.2 (C-3), 88.3 (C-1'), 103.2 (C-1), 110.6, (CIV-iPrd), 114.8 (C-4', CIV-iPrd), 127.2 (C-0'), 127.5 (C-p'), 129.1 (C-m'), 142.0 (C-n'), 143.8 (C-5'), 162.4 (C-6'), 186.2 (C=S) ppm. MS (IS): m/z = 548.5 [M + H]<sup>+</sup>.
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